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Prescription opioid abuse, pain and addiction: Clinical issues and implications

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Abstract

Issues—Prescription opioid misuse in the USA has increased over threefold since 1990 to epidemic proportions, with substantial increases in prescription opioid use also reported in other countries, such as Australia and New Zealand. The broad availability of prescription pain medications, coupled with public misconceptions about their safety and addictive potential, have contributed to the recent surge in non-medical use of prescription opioids and corresponding increases in treatment admissions for problems related to opioid misuse. Given competing pressures faced by physicians to both diagnose and treat pain syndromes and identify individuals at risk for addictive disorders, the use of opioids in the treatment of pain poses a significant clinical challenge.

Approach—This paper reviews the interaction between pain and opioid addiction with a focus on clinical management issues, including risk factors for opioid dependence in patients with chronic pain and the use of assessment tools to identify and monitor at-risk individuals. Treatment options for opioid dependence and pain are reviewed, including the use of the partial μ agonist buprenorphine in the management of concurrent pain and opioid addiction.

Implications—Physicians should strive to find a reasonable balance between minimising potential adverse effects of opioid medications without diminishing legitimate access to opioids for analgesia.

Conclusions—The article discusses the need to identify methods for minimising risks and negative consequences associated with opioid analgesics and poses research directions, including the development of abuse-deterrent opioid formulations, genetic risk factors for opioid dependence and opioid-induced hyperalgesia as a potential target for medication therapy.

Keywords

pain management; opioid dependence; buprenorphine; addiction; medication

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Introduction: opioids, the terribly good medications

Studies of drug abuse trends in the USA indicate that non-medical use of prescription opioids has increased over threefold since 1990 to epidemic proportions [1], with substantial increases in prescription opioid use also reported in other countries, such as Australia and New Zealand [2–4] representing a significant public health problem. As of 2008, an estimated 13.8 million people aged 12 or older had used oxycodone for non-medical reasons at least once during their lifetime [5]. Treatment admissions for prescription opioid abuse increased 400% from 1998 to 2008, escalating from 52 840 in 2003 to 120 877 in 2008, according to the most recently available data from the Treatment Episode Data Set [6,7]. In other countries, prescription opioid use has also substantially increased in recent years. For example, Australia experienced a 40-fold increase in oral morphine from 1990 to 2006, and an almost fourfold increase in oxycodone between 1990 and 2003 [4]. The broad availability of prescription pain medications, coupled with public misconceptions about the safety and addictive potential of these medications relative to illicit opiates, are factors contributing to the recent surge in non-medical use of prescription opioids [8].

Use of opioids other than as prescribed can take several forms: misuse, abuse or dependence as defined by the DSM-IV-TR (i.e. ‘addiction’). Physiological dependence, which involves the presence of tolerance and withdrawal symptoms, may occur even at prescribed doses in non-addicted individuals. Although only a small minority of individuals prescribed opioids for chronic pain will subsequently develop abuse or addiction [9], increased rates of substance use disorders have been well documented in long-term prescription opioid users relative to individuals who do not use opioids [10,11]. The presence of depression or anxiety disorders may contribute to increased risk of substance use disorders among long-term opioid users [12].

Other potential adverse effects associated with opioid medication use include respiratory suppression and overdose, medication interactions, infectious disease transmission (with intravenous use), and engagement in other risky behaviours, including alcohol and other drug abuse. When prescribing opioid medications, physicians must weigh these risks against the known benefits of opioids in the management of pain. Not only are opioids the most potent medications available to treat the majority of severe pain conditions, physicians are under increasing pressure to identify and adequately treat pain in order to minimise suffering and improve functioning. Pain is a presenting complaint in over 80% of visits to physicians and contributes to significant health-care costs, yet pain is often underrecognised and inadequately treated in primary care settings. Over the past decade, an international effort has developed to improve pain assessment and management, and pain screening has been labelled as the ‘fifth vital sign’ [13,14].

The appropriate use of opioids in treating pain disorders poses a significant clinical challenge and dilemma. The role of opioid medications in the treatment of pain, particularly chronic non-malignant pain, remains a controversial subject. Policymakers have promulgated much of this controversy, which has produced ancillary effects on clinical practices that have swung like a pendulum in reaction to the trends of the times. As prescription opioids have become more widely available to address the problem of

undertreated pain, abuse and diversion of these medications have been on the rise [15]. Pain may contribute to the development of opioid abuse and addiction, which may emerge after a period of legitimate use of opioids as prescribed for analgesia. As noted by Trafton and colleagues [16], chronic pain creates a set of implications that must be considered in the course of managing addiction because the presence of pain may be a factor promoting drug-seeking behaviour, increasing depression and anxiety and resultant drug use, and reducing quality of life.

Significant levels of opioid diversion activities appear to occur in the supply chain—Internet-based pharmacies, pilfering from distribution centres and in-transit theft [17–22] as well as via prescriptions written by physicians but subsequently used other than as prescribed, where patients provide unused medications to relatives and friends or simply hoard the drugs for later use themselves or subsequent distribution to others [23]. To counter recent trends in abuse and diversion, long-acting opioid formulations have been developed, and other monitoring and control measures are in place to counter diversion. In a recent review of the safety and efficacy of long-acting opioid formulations in the treatment of chronic non-malignant pain, however, insufficient evidence was found supporting the efficacy and safety of long-acting medications relative to short-acting opioids [24]. More recently, pharmaceutical companies are moving forward in the development of abuse-deterrent opioid formulations. Some of these formulations involve technologies that prevent the release of active opioids when pills are crushed or when chemical extraction procedures are initiated. Others involve the use of prodrugs or the combination of opioid agonists and antagonists in a single formulation to deter use by injection [15].

The complexities of opioid misuse, pain and opioid-based medication indicate a need for greater education as well as for evidence-based guidelines that reflect current research and that are practicable in the office setting. From the perspective of addiction medicine clinicians, the presence of pain must be recognised and addressed. That analgesia is necessary cannot be ignored. Alternatives to opioid medications do exist, including NSAIDs and tricyclics as well as other non-opioid medications, such as gabapentin, pregabalin and valproic acid. Fortunately, there are effective approaches to the management of concurrent opioid addiction and chronic pain, as discussed below.

Managing opioid addiction and pain

Research has long demonstrated that patients with no prior history of opioid abuse treated with opioid pain medications over extended periods do not experience euphoria—these patients are therefore unlikely to become addicted [1]. Still, there is a risk that a small percentage (3.27–11.5%) of patients treated with opioids for chronic pain may develop addiction or abuse with negative consequences, complicating the management of chronic pain [9]. Patients with co-occurring pain and opioid use disorders are often treated by clinicians lacking sufficient training in addiction; furthermore, adequate empirical guidelines for managing pain while addressing opioid dependence are not readily accessible to the medical community.

Tools that clinicians should find useful in guiding opioid use for chronic pain management are available in recently published guidelines, such as those produced by the Royal Australasian College of Physicians [4] and the American Pain Society and Academy of Pain Medicine [25]. The authors recommend careful assessment of the patient, obtaining a formal, signed informed consent to ensure the patient's understanding of opioid risks and benefits, and a review of the treatment plan and expectations. In line with the development of 'universal precautions' [26], a thorough risk assessment is advised before initiating chronic opioid therapy to evaluate a patient's potential liability for developing opioid abuse or dependence. The authors note, however, that this task 'is a vital but relatively undeveloped skill for many clinicians', citing work by Passik and Kirsh [27], which set forth 'predictors' that were likely to be associated with patients' future addiction problems stemming from opioid pain medications. The presence of prior substance abuse in the patient and the patient's relatives can be one of the most telling 'red flags' of an addiction proclivity. Patient-administered instruments that can be used as approaches to identify risk of drug misuse include the revised Screener and Opioid Assessment for Patients with Pain [28] and the Opioid Risk Tool [29]. A clinician-administered assessment tool is the Diagnosis, Intractability, Risk, Efficacy instrument [30]. Similar guidelines are available from the Royal Australasian College of Physicians [4].

In addition to screening tools and precautionary measures, a more enforcement-oriented approach has been espoused by regulatory agencies, particularly the US Drug Enforcement Agency, the United Nations Office on Drugs and Crime, and the US Food and Drug Administration (FDA). An FDA-mandated 'Risk Evaluation and Mitigation Strategy' (REMS) will address the risks and benefits of some opioid medications and describe requirements and procedures to reduce misuse of opioid medications. A brief discussion of the FDA's REMS appears in the *Discussion*.

Beyond greater controls on sourcing and prescribing, developing skills in addiction medicine is an optimal approach for mainstream physicians, even if clinically useful screening tools are available. Integration of addiction treatment into primary health-care systems is a priority recently identified by the US Office of National Drug Control Policy in order to increase accessibility of treatment services [31]. Patient care may be compromised by schisms that exist within the specialty sector, particularly when services are not integrated between pain management clinicians and addiction specialists, as illustrated by the following case example:

> A 32-year-old male with chronic pain and disability since sustaining significant back injuries three years ago has been terminated from care by his pain doctor upon exhibiting signs of addictive behavior, including requests for early medication refills and increased opioid doses. The patient is referred to an addiction specialist, who diagnoses the patient with opioid dependence and recommends inpatient detoxification. After completing detoxification and agreeing to a behavioral treatment program, the patient reports significant ongoing pain and cravings for opioids. Given that his new clinician lacks expertise in pain management, a new comprehensive treatment plan addressing inadequate pain control must be considered.

The case above highlights the importance of close communication between specialty treatment providers to establish continuity of care, as well as the need to develop a multimodal, individualised plan of care to meet the unique treatment needs of each patient. Integrated treatment with adjunctive psychotherapeutic interventions has been put forth as a recommendation in the APS/ASAM guidelines, particularly for treatment of individuals with both chronic pain and impaired functioning or psychological distress. For patients on chronic opioid therapy who have been identified as 'high risk' for addiction, consultation with a mental health or addiction specialist is also strongly recommended [24].

Medication-based treatment for opioid dependence and pain

Current pharmacotherapy for opioid addiction relies on two 'substitution' or 'maintenance' medications—methadone and buprenorphine—administered to help individuals attain and maintain abstinence from illicit opioids and thereby reduce addiction-related behaviours. Methadone, a full μ opioid receptor agonist with a half-life of 15–60 h, has variable pharmacokinetics necessitating slow and careful dose escalation by experienced clinicians as rapid titration may be associated with increased risk of accidental overdose death. Long-acting opioids, such as methadone, may be useful in promoting medication adherence and more consistent pain control relative to shorter-acting opioids [25].

Although treatment with buprenorphine has long been provided in office-based settings in Australia, the UK and other European countries, the approval of buprenorphine for the treatment of opiate/opioid dependence in the USA represents the first time in over 80 years that pharmacotherapy for opioid dependence can be provided by private physicians in office-based practice, outside the confines of traditional narcotic treatment programs. The benefits of this advantage have yet to be fully realised. As a partial μ opioid receptor agonist and a κ receptor antagonist, buprenorphine has a greater safety profile than other full μ agonists, such as methadone. At higher doses, the effects of buprenorphine plateau, limiting both dose-dependent euphoria and respiratory depression [32]; recent evidence suggests that a ceiling effect for analgesia, however, does not occur [33,34]. Successful outcomes of buprenorphine pharmacotherapy alone (i.e. patients becoming or remaining opiate free) could be improved upon [35,36]. Although buprenorphine has proven to be a very effective medication, the problem of noncompliance with orally administered buprenorphine remains a major concern, compounded by diversion and misuse. Long-acting depot buprenorphine (e.g. subcutaneous implant as Probuphine®) poses a promising means of addressing these issues.

For many patients with comorbid pain and opioid dependence, buprenorphine may well be the preferred pharmacotherapy, given its safety, its ability to suppress opioid-seeking behaviour and its analgesic effects. Non-opioid medication treatment options include NSAIDs, tricyclic antidepressants, anticonvulsants, duloxetine, topical agents (e.g. lidocaine patch), muscle relaxants (e.g. methocarbamol, cyclobenzaprine) and interventional procedures (e.g. peripheral nerve blocks, steroid injections, spinal cord stimulators). For all patients, consideration of adjunctive non-pharmacologic treatment modalities is warranted, including cognitive behavioural therapy and other psychotherapeutic interventions [25,27]. Other non-pharmacological therapies that may be used in combination with medications

include physical therapy, biofeedback, massage therapy, relaxation training, and heat or cold applications [27].

Discussion and conclusion

Balance for the best medicine

The resolution of controversy surrounding opioid medications is a question of finding a reasonable balance to minimise potential adverse effects without diminishing legitimate access to opioids for analgesia. That approach is espoused, for example, in US FDA language regarding opioid medications—'FDA recognises the need to achieve balance between appropriate access and risk mitigation'—although many entities are competing to get their interests favourably weighed in striking that balance. In April 2009, the FDA announced their position on implementing an REMS pertaining to certain opioid medications (including long-acting and extended-release generics and brand name products formulated with fentanyl, hydromorphone, methadone, morphine, oxycodone or oxymorphone). The FDA can require an REMS to ensure that the benefits of drugs continue to outweigh the risks. On 10 February 2009, the FDA Office of Special Health Issues and the Center for Drug Evaluation and Research held a stakeholders meeting entitled, 'FDA Regulatory Process and Standards for Review and Approval of Opioid Analgesics; An Educational Primer and Conversation'. Its summary noted:

> Clearly, opioid products are at the center of a major crisis that has resulted in abuse, misuse, and death. A balance needs to be achieved between adequate pain control and managing the risks of these powerful drugs. The process of finding this balance will require the engagement of all stakeholders, including pain patients, patient advocates and the pain-treating medical community. ([37], pp. 1–2)

The still-developing REMS will emphasise more stringent arrangements controlling prescribing physicians' practices to lessen opportunities for misuse of opioid medications. While reasonable, that element of REMS could not address improper non-medical use of opioids occurring when patients provide their opioid medications to friends or family members, which accounts for 71% of reported sources, according to the US National Survey of Drug Use and Health [5]. New regulations on prescribing would not greatly influence this vector of drug misuse, although 'patient education' has been considered as part of the REMS approach.

Recognition of unresolved issues, such as the example above, has led the FDA to announce the re-opening of the opioid REMS comment period through 19 October 2010. That the FDA and stakeholders (including the Drug Enforcement Agency, manufacturers, physician groups and patient activists) are striving to find this balance is encouraging, and clinicians can take heart that an open and rational approach will continue.

At this point in our understanding of opioid addiction and its treatment, largely based on past and ongoing research but also informed by clinical experience, the authors are confident that opioid addiction concurrent with chronic pain can be effectively managed. Clinically useful therapies exist and should be more broadly implemented, including non-medication-based treatments and abuse-deterrent opioid formulations. A medication-based approach

using the partial agonist buprenorphine should be considered for opioid addicts who also have chronic pain, together with adjunctive behavioural or other non-pharmacological treatments. Given the wide variability in patient characteristics, however, the management of concurrent pain and addiction should be individually tailored. For example, while all patients are at risk of relapsing to opioid misuse, even while on substitution medication, some may be more susceptible because of presence of pain; in such patients, a higher level of clinical supervision may be necessary.

Possible future considerations

An interesting phenomenon occurring at the nexus of pain and addiction is opioid-induced hyperalgesia (OIH), which can arise as a consequence of long-term usage of opioid medications and opiate street drugs as well [38]. The mechanisms underlying the syndrome of increased sensitivity to pain stimuli are still topics of research, but preclinical work [39,40] suggests that there may be pharmacotherapeutic approaches to countering development of OIH. And while the role of OIH in pain and in addiction remains unclear, medications capable of providing analgesia without inducing hyperalgesia are likely to be of clinical importance. Agents that can reverse established hyperalgesia induced by other opioids will likewise be of clinical interests. One such medication that deserves further examination for its potential in this regard is buprenorphine, which has shown some preliminary promise to provide ‘anti-hyperalgesia’, likely attributable to its κ effect. There is also some preliminary suggestion that gabapentin may reverse OIH [41].

Another topic of interest in assessing a pain patient’s risk of developing opioid addiction is the genetic disposition. Genetic polymorphisms have been associated with vulnerability to opioid dependence [42]. While a genetic screen for all patients would be impractical, there may be a reasonable justification for such a procedure in some cases where other risk factors are apparent. Identification of at-risk individuals would yield opportunities for targeted prevention efforts and would provide valuable information for clinicians when assessing opioid medication risk and determining pain management approaches for individual patients. Genetic research in this area is in early stages, however, and medications that might target polymorphisms to alter phenotypic expression are a long way off.

Finally, an interesting proposition under consideration has been whether we can separate the analgesic effect of opioid medication from its effect on mood via the reward circuit. Research with NK1 antagonists suggests that that might be possible [25], but it is uncertain whether patients or physicians will embrace such an agent to make it clinically useful.

In the end, we must acknowledge that the philosophical orientation of the clinician greatly influences decisions about prescribing opioid medications for pain patients, whether an assessment of proclivity to misuse is based on guideline-based assessment tools, on clinical experience or on a combination of all approaches. If the current mainstream approach in Western medicine is, at the very least, to discuss with patients the availability of opioid medications as a potential means of addressing pain, then falling within that approach is a range of clinician-specific variations in prescribing practices. Suffice to say that patients in pain need to be made aware of opioid risks and benefits, as *caveat emptor* does apply. The increasingly influential moves to install universal precautions and risk assessment paradigms

send a loud message to clinicians and pharmaceutical companies that they must adhere to *caveat venditor*—let the seller beware.

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